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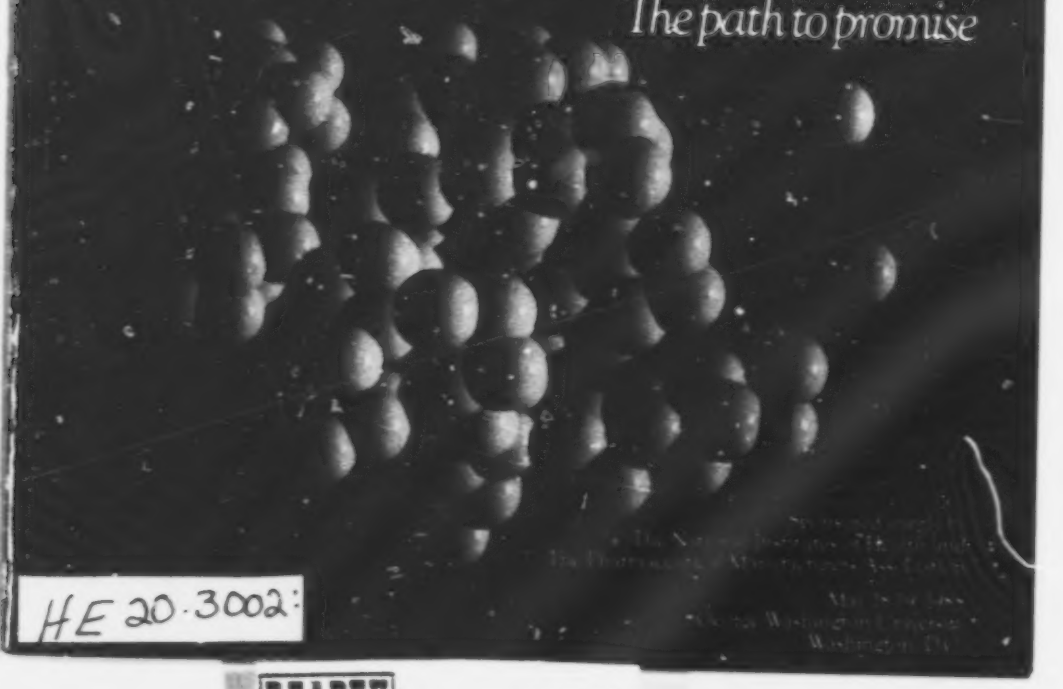
REPORT OF THE NATIONAL CONFERENCE ON ORPHAN DRUGS

The path to promise



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REPORT OF THE NATIONAL CONFERENCE ON ORPHAN DRUGS

The Path to Promise

The National Institutes of Health and
The Pharmaceutical Manufacturers Association

May 18-19, 1988
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Washington, D.C.

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PREFACE

The Orphan Drug Act of 1983 established a clear national commitment to assure the availability of drugs for diseases or conditions that occur so infrequently in the United States that there is no reasonable expectation that the costs of developing and marketing drugs for such diseases will be recovered through revenue from sales.

In recognition of their respective roles and responsibilities in achieving this national goal, the Pharmaceutical Manufacturers Association and the National Institutes of Health sponsored this conference to:

- Acknowledge the importance of the partnership that has been forged between Federal health agencies, pharmaceutical companies, and universities to promote and facilitate the discovery, development, and marketing of drugs for rare diseases and to examine the nature and effectiveness of this alliance
- Assess recent accomplishments, current activities, and plans for future efforts of each of the partners in this innovation process
- Identify potential obstacles that may exist to the continued and accelerated progress of activities in this area, and
- Explore emerging opportunities to promote additional cooperation designed to achieve advances against rare diseases

While this conference was intended primarily to explore and strengthen the relationships that exist among the principal sponsors and performers of research and development leading to the discovery and commercialization of technologies to combat rare diseases, the program was organized to reflect the key roles that are played by:

- Congress, in identifying structural impediments to technological innovation and enacting legislation to promote and facilitate the discovery and commercialization process
- Regulatory agencies in attempting to achieve an appropriate balance between the need to provide adequate safeguards against untoward health effects of new products and the need to encourage innovation, and
- Voluntary health organizations, in serving as advocates to promote the development and introduction of new technologies

for the diagnosis, treatment, and prevention of rare diseases.

This conference was conducted in the hope that the information and recommendations emanating from the meeting will benefit those who are involved actively in combating rare diseases and will stimulate others to join in this continuing effort.

PROGRAM PARTICIPANTS

Dr. Carolyn R. Asbury: Robert Wood Johnson Foundation

Dr. Daniel L. Azarnoff: D. L. Azarnoff Associates, Inc.

Dr. Barry A. Berkowitz: Smith Kline & French Laboratories

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Dr. Floyd Brinley, Jr.: National Institute of Neurological and Communicative Disorders and Stroke, NIH

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Dr. Robert S. Janicki: Abbott Laboratories

The Honorable Nancy Landon Kassebaum: United States Senate

Mr. Gerald F. Meyer: Food and Drug Administration

Ms. Abbey S. Meyers: National Organization for Rare Disorders

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Dr. W. Leigh Thompson: Eli Lilly and Company

Dr. David Valle: Johns Hopkins Medical School

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INTRODUCTION

Scientifically, this is a period of unprecedented opportunity for drug development, with technological breakthroughs providing new means for discovering treatments for heretofore incurable diseases. However, soaring costs for developing new drugs and bringing them through regulatory review to market present one of the most serious challenges to the U.S. and worldwide health care industry. Moreover, because many diseases affect only very small numbers of individuals, there is less economic incentive for pharmaceutical manufacturers to develop products for treating such relatively rare diseases. In the United States, however, the Orphan Drug Act of 1983 established a national commitment to make drugs available for rare conditions, recognizing that special incentives are needed when revenues from product sales cannot be expected to compensate for development and marketing costs of new drugs.

As part of this commitment, a new partnership has been formed among federal health agencies, pharmaceutical companies, and academic institutions. As one major contributor to this partnership, the National Institutes of Health has continued to foster a traditional interest in human diseases that now fall under the "rare" disease classification, defined by the Orphan Drug Act as having a prevalence of less than 200,000 cases. Continued support by NIH of university-based researchers encourages a broad and expanding base of new scientific information necessary for better understanding and combatting such diseases. And a new cooperative spirit with both traditional drug manufacturers and new biotechnology companies is helping to link more closely the academic, private, and federal sectors--better ensuring that their complementary strengths are being channeled efficiently.

In recognizing this already heightened cooperation and in planning ways to further enhance it, NIH and the Pharmaceutical Manufacturers Association joined in sponsoring a conference on orphan drugs. Although intended principally to assess current activities, identify potential obstacles, and explore emergent opportunities, the conference also reviewed key roles played by the Congress, regulatory agencies, volunteer health organizations, advocacy groups, and academic researchers, as well as other such groups with special interests in this topic.

There is wide agreement that the Orphan Drug Act is working--indeed, working very well. Already more than 200 drugs have been given orphan status, with 56 drugs achieving that status in 1987. Altogether at least 24 orphan drugs --eight within 1987--have been approved by the Food and Drug Administration, taking an average of 10-11 fewer months to move through the regulatory system than other new drugs, according to FDA officials. At an administrative level, FDA has taken several steps to encourage

wider and more efficient use of the Act, and recent amendments to the Act also are encouraging further expansion of the program.

On another very important level, the Orphan Drug Act has offered new hope to the nearly 20 million Americans suffering from rare diseases or disorders, according to Kansas Senator Nancy Kassebaum, who helped shepherd the legislation through Congress. "They now know that the same system which brought forward penicillin and the polio vaccine and cancer therapies is working for them as well," she says. "It has been said there is no medicine like hope--no incentive so great and no tonic so powerful."

SCIENTIFIC STAGE IS SET FOR PROGRESS

The scientific stage is set for making significant progress in understanding and combatting many rare diseases. Impressive developments in biotechnology, molecular biology, and in the more traditional areas of biochemistry are providing researchers with new analytical tools, many of which are being used in developing therapeutic approaches and novel products.

In addition, the current revolution in genetics is bringing forth many important insights into the more than 3000 known human genetic diseases, most of which affect very small population groups. The field of human genetics is poised to expand even more rapidly as the biomedical research community takes on the challenge of mapping and eventually sequencing the human genome.

Added to these efforts is the rapidly developing area of structural biology, with its improving capacity to use data from x-ray and nuclear magnetic resonance studies along with the technologies offered by computer graphics to rapidly build detailed and informative molecular models. Thus, for example, for researchers developing new antiviral agents, such approaches are leading to a more systematic and rational design of products for rare viral diseases instead of reliance on a purely empirical approach.

Besides some of the relatively rare genetic and viral diseases, various neoplasms, immune system disorders, and neurological syndromes also occur so infrequently as to be classified as orphan diseases. By supporting both fundamental and applied programs in all these areas, NIH sponsors a very broad range of intramural and extramural research activity within the category of orphan diseases.

Genetic and Biochemical Disorders

Although geneticists have classified more than 3000 specific human genetic disorders, there may be many more yet to be discovered. Some authorities believe there could be at least as many disorders as there are functioning human genes--an estimated 100,000. The disorders range in severity across a spectrum: from benign, to intermittent, to chronic and long-term, to severe and even fatal, according to David Valle of Johns Hopkins University Medical School in Baltimore, Md. Perhaps the best known disorders are "monogenic," relatively rare and often involving only a single nucleotide change within a complex gene for a cellular protein. Other broad types of genetic disorders include multifactor (meaning at least several genes) and grosser chromosomal abnormalities.

The prototype monogenic disorders include an assortment of inborn errors of metabolism, usually due to the malfunction of a single type of catalytic protein, or enzyme, within the body. The homozygous frequency of some of these well-known disorders varies considerably within the U.S. population--ranging, for example, from about one per 600 for sickle-cell anemia, to one in about 13 thousand for cystic fibrosis, to one in 100 thousand for the maple syrup urine disease. Often a particular disorder has a much higher frequency within a specific segment of the population.

Phenylketonuria (PKU) is one of the better known monogenic disorders, one for which virtually all newborns in the United States are screened. The disorder was at first thought to involve only a single specific defect of the enzyme called phenylalanine hydroxylase, which is responsible for metabolizing a particular aromatic amino acid. Recently, however, researchers at Baylor Medical School in Houston learned that at least six distinct mutations can occur within the complex gene for this enzyme. Currently, the only treatment available for newborns with this disorder, which leads to abnormal brain development and mental retardation, is to follow a special diet to restrict intake of the amino acid phenylalanine.

PKU is a relatively common genetic disorder affecting thousands of individuals. Other genetic syndromes, such as gyrate atrophy of the retina, are much rarer--affecting only a few dozen people in the United States, and perhaps only a few hundred patients throughout the world, according to Valle. "It is the only known eye disease with a biochemical handle," he says. His laboratory has recently uncovered part of the molecular mechanism that explains how this degenerative disease can cause blindness. A single codon change within the gene for an enzyme that metabolizes the amino acid ornithine gives rise to the syndrome, he and his colleagues find. That change, or mutation, may occur at one of several different sites within the gene. So far, such information has led to improved methods for diagnosing the

condition and to a better understanding of its pathophysiology. As yet, however, clinical researchers have not developed a clear-cut therapy. Moreover, it is still doubtful whether dietary restriction of ornithine (and the related amino acid, arginine) intake will provide clinical benefits.

One general approach to treating many such genetic disorders is to replace the defective (or absent) protein. For several well-known diseases, including diabetes and several forms of hemophilia, such therapy has become essential and virtually routine. But for many other genetic disorders, including a variety of orphan diseases, therapies are still in different stages of development. Gradually, as biochemical requirements are better defined and biotechnology continues to make scarce proteins easy to produce in large quantities, more treatments will become available for these rare syndromes. For instance, use of alpha$_1$ antitrypsin as protein replacement therapy to treat some types of hereditary emphysema is expected soon to become widely available, according to Robert Desnick who is chief of the division of medical genetics at Mt. Sinai Hospital in New York.

Other similar efforts, including enzyme replacement therapy for Gaucher's disease and Fabry's disease, have proved trickier to master, particularly because the protein being administered to patients in either case must have sugar molecules properly attached to it. Although biotechnology is providing new ways to produce properly modified proteins, their safety and efficacy must still be carefully tested, with the most difficult standard of proof being the requirement for long-term clinical trials.

Perhaps one of the most promising adaptations of enzyme replacement therapy now being studied involves a chemical modification in which polyethylene glycol (PEG) is attached to the missing protein molecule before it is administered therapeutically. For example, Michael Hershfield at Duke University Medical Center in Durham, N.C., and his collaborators are testing this concept to treat adenosine deaminase deficiency, a rare (one in one million) genetic defect that causes a severe combined immunodeficiency disorder. Thus, when an individual is missing this enzyme, purine nucleotide concentrations rise too high, leading to deterioration of the immune system. Administering the purified but unmodified enzyme to patients is ineffectual because it is cleared too rapidly from the plasma. However, when the enzyme is modified by attaching PEG molecules, it remains in plasma for at least a week following injection. So far, only a very small number of children with this disorder have been treated, and "all the kids are responding," Hershfield says. With repeated injections, the enzyme levels remain high in plasma, and at least some of the immune functions missing in such patients seem to be restored.

An alternate long-term goal for treating such monogenic disorders involves direct gene therapy, notes Martins Eglitis, a senior staff fellow in the National Heart, Lung, and Blood Institute at NIH. A considerable effort is now being devoted to genetic manipulation of bone marrow cells--introducing replacement genes in retrovirus vectors into such cells and then putting them back into the body. Despite limited success in experiments on rodents, early tests of this technology in monkeys have proved disappointing. However, researchers are continuing to explore new techniques to overcome these current difficulties, many of which seem to reflect the need for a much deeper understanding of how bone marrow cells are propagated.

Complex Neurological and Immune Disorders and Cancer

Epilepsy is a complex and poorly understood set of neurological disorders, which are undoubtedly multifactored in their origins. Although about 1% of the U.S. population has epilepsy, there are several distinct forms of the disease and available drugs typically do not work for all the different forms of the disease. Hence, treatments for this group of diseases may be designated orphan drugs, according to James Cereghino of the National Institute of Neurological and Communicative Disorders and Stroke at NIH.

The history of drug development to control epilepsy provides a fascinating account of occasional remarkable discoveries, frequent frustration, and exhaustive empirical searches. In the late 1960's, NIH embarked on a massive screening program to examine potential drugs made available from academic and industrial researchers. According to Cereghino, more than 13,000 compounds have undergone preclinical testing, primarily at the University of Utah by Ewart Swinyard; 2000 of them moved into phase I clinical testing; of those compounds, about 475 continued through later phases; and about 20 have gone on to full-scale clinical trials. None of the entrants has come all the way through the system to full clinical use, although several of the final 20 are continuing in clinical trials, he notes. Despite frustrations that such a full-scale effort has not turned up more in the way of promising new drugs, it provides a model cooperative program, showing how the resources of NIH, industry, and universities can be marshalled in the search for useful drugs.

Recently, researchers have begun using positron emission tomography (PET) to study epilepsy, according to Thomas Chase, also of NINCDS at NIH. A powerful but still very new technology, PET requires a dedicated team of nuclear chemists to provide analytic chemicals as well as a complex instrument to gather and analyze emission data from specific regions of the brain. Depending on the chemical entity being used, investigators can derive a precise picture of brain chemistry and physiology in

action. For example, researchers can now monitor both the sequence of events and their location within the brain during an epileptic seizure. Eventually, such information could help in designing and evaluating new drugs. Similarly, PET scans are helping neurologists understand why DOPA treatment often becomes gradually less effective for the treatment of Parkinson's disease.

Although perhaps less daunting than the central nervous system, the immune system also is prone to complex disorders. A number of these "accidents of nature" fall under the rubric of orphan diseases, says biochemist Allan L. Goldstein of the George Washington University School of Medicine. Although rare, some of these syndromes are difficult to distinguish from acquired immunodeficiency syndrome (AIDS), and indeed they can provide important insights into how human immunodeficiency virus infections can undermine the essential protection ordinarily provided by the immune system. A group of peptides known as thymosins have been given orphan drug status, and they are being tested as treatments for several rare immunodeficiency disorders as well as for improving immune responses among the elderly and also for treating individuals with chronic cases of hepatitis B, Goldstein notes.

As with many neurological and immune disorders, cancer also represents a complex family of diseases, many of which are rare within the U.S. population and therefore qualify as orphan diseases, according to Robert Wittes of the National Cancer Institute at NIH. A rule of thumb is that the rarer the cancer, the greater the likelihood it can be cured. This is due partly to a quirk of fate and partly to the biology of cancer, he notes. The search for antineoplastic agents involves both a massive screening program as well as a more-targeted review of biological agents, such as lymphokines and cytotoxic agents, now made available because of advances in biotechnology. A whole variety of cooperative agreements is helping to ensure that these many new agents are tested against a wide variety of rare and more common neoplasms.

According to NIH Associate Director for Science Policy and Legislation, Jay Moskowitz, many of the recent advances and new scientific opportunities discussed at the conference are of a sufficiently generic nature to permit application to a wide variety of diseases, including a host of rare diseases. He suggests, for instance, that (1) advances growing out of biotechnology have established entirely new paradigms for drug development, including drugs for rare diseases; (2) new approaches to detecting the specific products produced by faulty genes are serving to guide the development of a range of drugs to repair inherited defects in the body's biochemical machinery--defects often found in rare diseases; and (3) the application of structural biology to the development of antiviral drugs has

profound implications for all viral diseases, including many rare diseases.

GENERAL POLICY ISSUES

The U.S. effort in drug development is enormous but also resource intensive. For instance, in 1987 the U.S. pharmaceutical industry invested about $5.4 billion in research and development programs, according to PMA president Gerald Mossinghoff. Moreover, it costs about $125-150 million to bring each new drug to market, and the effort takes from 7 to 13 years. Meanwhile, a shortage of qualified scientists and technicians may be developing--a prospect that could make the difficult process of drug discovery and development considerably more problematic in the future, particularly insofar as orphan drugs are concerned. Nonetheless, the Orphan Drug Act of 1983 has provided a much needed stimulus and a new outlook for a field that had been badly neglected. Although there has been an historical commitment to orphan drug discovery and development by the pharmaceutical industry prior to the enactment of the orphan drug legislation in 1983, a recent PMA survey revealed that 14 research-intensive companies made an average investment of almost $14 million for a total of over $183 million since the enactment of this legislation.

Although the stipulations of the Orphan Drug Act are clear cut, implementing them has not always been so straightforward. For one thing, according to Carolyn Asbury of the Robert Wood Johnson Foundation, none of the large federal data bases systematically distinguishes orphan diseases from all others. Hence, ambiguities can arise when considering a particular syndrome's proper status. Moreover, because there is no comprehensive data base, keeping track of how much is spent on orphan drug research and development, what the best leads are, where opportunities for collaborations may be found, and other potentially useful matters are not straightforward tasks.

Moreover, in part because of rapid advances in biotechnology, some troublesome patent issues have arisen. The ownership of intellectual property rights and the preparation of virtually identical products by competing companies are but two of the problems that have come to light so far. The Act provides for a 7-year exclusive marketing period for an approved orphan drug. However, the perplexing possibility that competitors may be entitled to "shared exclusivity" of the marketing rights for a particular drug is one important but as yet unsettled issue that could have a significant impact on orphan drug development. The many patent disputes now pending in the biotechnology industry also could have a serious detrimental effect on orphan drug development.

The potential high cost of patent disputes is not the only serious threat of a financial drain on this field. For instance,

the general problem of product liability costs faced by the pharmaceutical industry is made even more threatening in the context of orphan drug development, where the payback expectations typically are more modest. Paradoxically, but no less worrisome to the families who depend on new orphan drugs, is the prospect that some of them may be made available only at very high costs--a practice that some critics claim is not in keeping with the spirit of the law.

Key Federal Programs

Several programs at NIH as well as a special office within FDA are helping improve the efficiency of new orphan drug development. In part, these new programs can be traced to the Federal Technology Transfer Act of 1986, which mandated government-wide changes that have taken somewhat different shapes within individual agencies. An additional mechanism for technology transfer between the federal government and the private sector is embodied in the small business innovation research (SBIR) program, which formed following legislation enacted in 1982 and recently extended through 1993. The Orphan Drug Act and subsequent amendments have established new offices and programs within FDA to encourage an active expansion of orphan drug efforts.

NIH is establishing a series of cooperative research and development agreements (CRADA) to encourage the practical development of scientific research, according to NIH associate director Philip S. Chen. Such agreements lay out terms for paying licensing fees and royalty income to federal investigators and their laboratories from commercial sales of technology they helped develop. The agreements also contain provisions for granting companies exclusive licensing rights for particular innovations. Such provisions have been deemed essential by industry representatives for encouraging full-scale development of particular projects. NIH has established a Patent Policy Board to oversee negotiations of these agreements and to prevent abuses developing.

The NIH SBIR program includes a 1.25% share of the agency's overall budget as a set-aside to support (through grants and contracts) projects that are intended to commercialize promising biomedical developments. The NIH program has been receiving up to 700 proposals and making an average of 400 awards with an aggregate total of $65 million per year, according to Lily Engstrom of the NIH Office of Extramural Research.

SBIR agreements must be concluded with small (fewer than 500 employees), for-profit, U.S.-owned businesses, Engstrom points out. And in other respects, the program is "very structured," meaning that most projects begin on a small-scale and undergo careful, repeated reevaluation as they build in size. Although

the NIH SBIR program now supports a wide variety of projects on rare diseases, it is "not ideal" for orphan drug development, Engstrom says. The reason is that successful SBIR projects are expected to generate profits, even substantial profits, whereas the Orphan Drug Act is intended to cover situations where high returns on investment are not anticipated.

Orphan products are being handled very efficiently within FDA, according to Gerald Meyer, deputy director of the agency's Center for Drug Evaluation. Although orphan drugs must meet standard criteria for being both safe and efficacious, they have on average been approved more rapidly than have other products, he says. Some of these improvements are due to the special role being played by the new office for orphan drugs at FDA. Unique within the regulatory agency, it helps in acting as an ombudsman when problems arise, notes program head Marlene Haffner of FDA.

In addition, the office runs a small grants program, with a current annual budget of $4.6 million that has been reauthorized to spend up to $15 million. This program puts the agency in the unusual position of being able directly to promote orphan drug research and development. Often, the agency has done so during the early phase of clinical trials for a new product, Haffner says.

Recent amendments to the Act also enlarge its scope. For example, jurisdiction has been extended to include "medical foods" needed by individuals with rare diseases and also special orphan medical devices.

One important general problem yet to be faced, Haffner continues, is the high cost of conducting rigorous toxicity studies, which orphan drugs must undergo just like any other drugs that come before FDA for approval. The FDA National Center for Toxicological Research in Jefferson, Arkansas, is considering doing all orphan drug toxicity studies on a fee-for-service basis.

Private, Volunteer, and Academic Sector Concerns

The traditional pharmaceutical and more recently formed biotechnology industries represent a diverse set of interests and abilities when addressing orphan drug-related issues. Although this diversity is itself of great value in the search for new drugs and devices, it also represents a new and growing challenge for regulatory agencies--particularly FDA. Thus, expanding research efforts within the industry, efforts that are bringing ever greater numbers of new products to FDA for evaluation, create a need for the agency itself to expand staff and resources to cope with the increasing work load.

Industry representatives and leaders from volunteer-supported health organizations point out that resource limitations at FDA may be creating "logjams" and thus inadvertently slowing progress. Moreover, the coordination among federal agencies could stand improvement, says Abbey Meyers of the National Organization for Rare Diseases. If improved, the problem of having a wasteful "patchwork of single disease centers" might also be addressed, she adds.

Meyers points to the high cost of human growth hormone, now designated an orphan drug for treating pituitary dwarfism, as perhaps the greatest problem that "could taint the whole orphan drug program." A family may pay $20,000-$30,000 per year for drug treatments for a child, a "major expense" that seems out of line with the intent of the Act, she argues. "We want [the industry] to make profits, but [it] must make the drugs affordable."

Nonetheless, biotechnology companies are bringing "fresh ideas to the discovery of new drugs, and considerable money is being spent on research looking into the etiology of diseases," says Daniel Azarnoff, president of Geritech, Inc. A particular company's efforts toward development of an orphan drug product must match closely with other scientific and manufacturing abilities within the organization, he adds. Otherwise, talents and resources become too thinly spread out. However, at least for the very large corporations, it helps when corporate planners can take "a world view...and be more eclectic," says Marvin Jaffe, senior vice president of medical affairs at Merck, Sharp and Dohme Research Laboratories. Such differences underscore why the search for orphan drugs is by no means uniform within the industry.

Size and past successes give the larger pharmaceutical companies the opportunity to do some "shifting among categories" of high-risk R&D projects, Jaffe continues. At least some of the time, the focus is more on the search for useful clinical products and less on their potential market size. "Understanding a rare disease of genetic origin...may lead to a greater understanding of a disease with wider prevalence," he points out. Thus, even though some projects may appear to be high risk with little potential for a profitable return, they may be justified because they provide valuable insights for other, more broad-based product development projects within the company.

According to Theodore Cooper, who is Chairman of the Board and Chief Executive Officer of the Upjohn Company, the ability of the pharmaceutical industry to achieve innovation in the development of drugs is influenced greatly by the overall state of biomedical research in this country. He notes that "if the nation's basic research foundation suffers, so will the industry which draws heavily from that basic research pool that is primarily supported by the National Institutes of Health and the National Science Foundation."

Burt Spilker of Burroughs Wellcome Company used his company as an example of how the activities of the pharmaceutical industry are contributing to the development of drugs for rare diseases. He noted that Burroughs Wellcome made 14 requests for orphan drug status on 11 drugs and received 11 approvals on 9 such drugs. Two of these drugs have been marketed, and two others are pending FDA approval for product licenses.

Greater support and recognition for clinical investigators also is needed, says Stanton Segal of the University of Pennsylvania School of Medicine. Investigators at academic institutions who have helped develop orphan drugs often have become cynical about the process because it has been so wearing. These "orphan physicians" would benefit if the infrastructure were improved and they were given the recognition and financial backing they deserve. With such improvements, the problem of recruiting new investigators may prove easier to solve, he adds. Naturally, universities and physician investigators must also do their parts in making improvements. For instance, although observant physicians often supply anecdotal information about the unexpected utility of a drug, they frequently have not been willing to develop more systematic information, Spilker points out.

The National Organization for Rare Diseases maintains a data base listing locations of patients with rare diseases, and the organization can arrange for free travel for pediatric patients. In addition, the organization shares disease prevalence data and tries to find information sources when data are lacking. According to Segal, such arrangements would work even better if regional centers for rare diseases were given stronger financial support.

CONCLUSION

Remarkably, in the very short period since the orphan drug legislation was enacted, an extraordinary level of consensus has built up in its support. Perhaps its most noteworthy feature is the balance it strikes between public and private sector needs, according to Senator Kassebaum. "On the one hand...there is a public policy purpose served by government in assuring that rare diseases and conditions are not ignored," she says. "At the same time, we have recognized that many of the tools for achieving this purpose lie in the hands of the private sector." Thus, by granting a seven-year period of marketing exclusivity to the manufacturer of a particular orphan drug, the private sector is provided "an extremely important incentive for the development of drugs that otherwise would not have been produced," she points out.

"The Orphan Drug Act offers a public benefit in order to achieve a public policy purpose," Kassebaum says. "Any company that takes advantage of that benefit has an obligation to honor the public responsibility it carries. The failure to do so can easily undermine the credibility of the Act, overshadowing the enormous good that it has accomplished. Overall, I believe this responsibility has been taken seriously."